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CASE REPORT

Nevoid basal cell carcinoma syndrome—case report and genetic study

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Nevoid basal cell carcinoma syndrome (also named Gorlin-Goltz syndrome) is a rare disease. Commonly seen features include multiple odontogenic keratocysts (OKCs), nevus-like basal cell carcinoma, and bifid ribs. Genetic alterations of the PTCH1 gene are associated with the disease. Herein, we report the case of a 15-year-old girl who presented with multiple OKCs, a bifid rib, ectopic calcification of the falx cerebri, and an arachnoid cyst of the cerebrum. No basal cell carcinoma was identified. In addition, a search for genetic alterations was performed on the patient. We identified a genetic mutation of C→T in exon 12 (c.1686 bp) and a G→C mutation in intron 13 (g.91665 bp) of the PTCH1 gene. Although a similar mutation in exon 12 was reported in a literature search, the mutation in intron 13 has not previously been reported. The patient has continued to be followed-up almost 3 years after the surgery with no recurrence of the OKCs or development of basal cell carcinoma.

Introduction

Nevoid basal cell carcinoma syndrome is an autosomal dominant inherited disease. The prevalence of the syndrome is estimated to be about 1 in 60,000. One of the major manifestations in these patients is multiple odontogenic keratocysts (OKCs) of the jaws, in addition to multiple nevus-like pigmentations which represent basal cell carcinomas. Other commonly seen clinical features include calcification of the falx cerebri, bifid ribs, palmar/plantar pits, and benign neoplastic changes in the brain.¹ Genetic alterations, including mutations, insertions and deletions, in the PTCH gene have been reported. Here, we document a case of nevoid basal cell carcinoma syndrome in a 15-year-old girl who developed

three consecutive OKCs in the mandible. In addition, the presence of a bifid rib and calcification of the falx cerebri were discovered. Computed tomography scan of the brain demonstrated a 1.5-cm arachnoid cyst in the right frontal lobe of the brain. A genetic sequencing study was performed on the patient to search for mutations in the PTCH gene.

Case presentation

The patient was a 15-year-old high school female student who came to the Oral and Maxillofacial Surgery clinic at Chung Shan Medical University Hospital in May 2006 with the chief complaint of swelling at the lower left anterior mucolabial fold

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for several months. An intraoral examination showed swelling of the lower anterior mucolabial fold, and also a missing lower left canine (#33). Extraorally, multiple nevus-like macules were noted across the face (Fig. 1). A panoramic radiograph was taken, and an impacted mandibular canine (#33) was noted to be surrounded by a well-defined radiolucent lesion and divergent roots of the first premolar (#34) and lateral incisor (#32) (Fig. 2). A clinical provisional diagnosis of a dentigerous cyst was rendered. The patient was scheduled to have the cyst enucleated, and the impacted #33 tooth was removed in July 2006. Histopathological evaluation of the specimen showed a cyst lined with keratinized stratified squamous epithelium and prominent palisading basal cells, suggestive of OKCs. In the meantime, radiographic examinations showed ectopic calcification of the falx cerebri (Fig. 3) and a bifid right fourth rib (Fig. 4). In addition, brain magnetic resonance imaging showed a possible arachnoid cyst with a greatest dimension of 1.5 cm in the right frontal lobe (Fig. 5). A full spinal radiograph showed marked scoliosis along the T spine (Fig. 6). Thus, a final diagnosis of nevoid basal cell carcinoma syndrome was made.



Fig. 1 Multiple pigmented macules and papules on the face of the patient.



Fig. 2 Initial panoramic radiograph shows a well-defined radiolucent lesion (arrows) associated with an impacted left mandibular canine (#33).

After surgery, the patient was placed under close radiographic follow-up. Three months later during follow-up, well-defined radiolucent lesions were noted around the left and right mandibular third molars (Fig. 7), although no clinical signs or symptoms were observed. Our clinical impression was OKCs for both lesions, and the patient was arranged to receive another cyst enucleation. Histopathologic evaluation of both specimens from the left and right lower mandibular third molar regions confirmed the clinical impression (Fig. 8). Almost 3 years after surgery, the patient continues to be under routine follow-up with panoramic radiographs, and no recurrence of OKCs has been noted, or basal cell carcinoma detected.

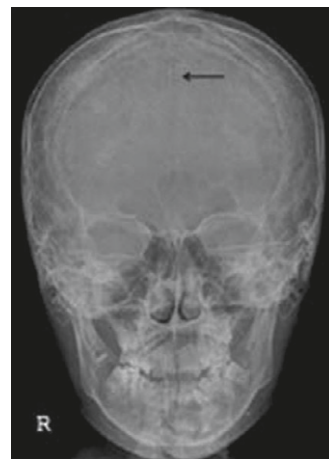


Fig. 3 Skull radiograph shows calcification of the falx cerebri (arrow).

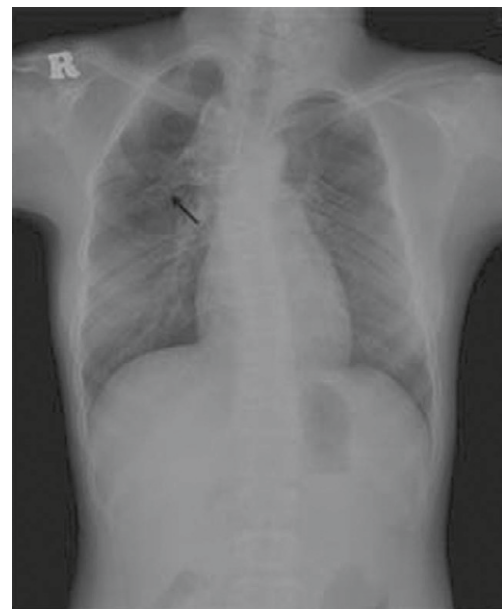


Fig. 4 Chest posteroanterior radiograph shows a bifid deformity of the fourth rib on the right side (arrow).

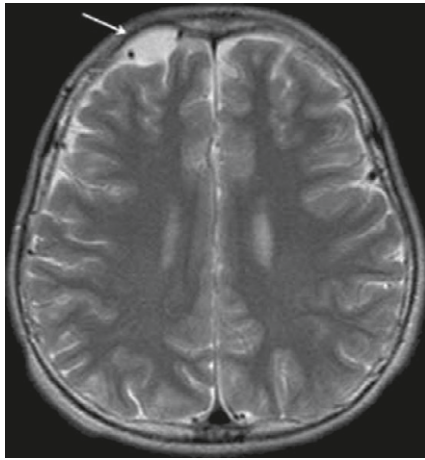


Fig. 5 Magnetic resonance imaging of the brain shows a 1.5-cm arachnoid cyst in the right frontal lobe (arrow).

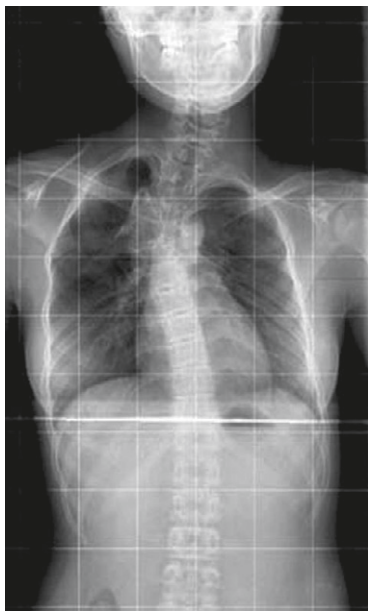


Fig. 6 Full-spine radiograph shows marked scoliosis at the T spine region.



Fig. 7 Additional well-defined radiolucent lesions noted during follow-up in the #38 and #48 areas (arrows).

Since different mutations of the PTCH gene have been reported in the literature with syndromic OKCs, a genetic study on mutations of the PTCH gene was performed. Whole blood was drawn from

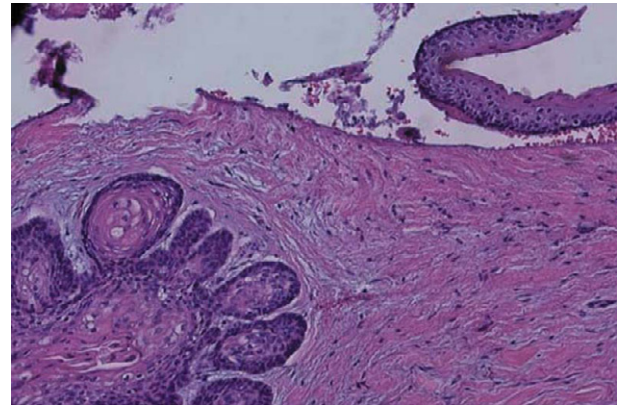


Fig. 8 Histopathological features show a cyst lined by parakeratinized stratified squamous epithelium with the notable presence of a satellite cyst.

the patient, and genomic DNA was prepared using a Blood Genomic DNA Purification Kit (GeneMark Technology, Tainan, Taiwan). The genomic DNA was then sequenced. Results showed a transition of C→T in exon 12 (c.1686bp) and a G→C in intron 13 (g.91665bp) (Fig. 9).

Discussion

Nevoid basal cell carcinoma syndrome is also termed Gorlin syndrome. It is an autosomal dominant inherited condition.¹ The chief components are multiple basal cell carcinomas of the skin, OKCs, intracranial calcification, rib and vertebral anomalies, and intracranial neoplastic change,¹ as presented in our case. Although no basal cell carcinoma was diagnosed in our case, she had many nevus-like papules on her face and thus will be closely followed-up.

Development of this disease is linked to mutations in PTCH, a tumor suppressor gene that was mapped to chromosome 9q22.1–22.33.^{2–5} The PTCH protein is the receptor for sonic hedgehog (SHH), a secreted molecule implicated in the formation of embryonic structures and in tumorigenesis. There are 24 exons in the PTCH gene, and genetic alterations including mutations, insertions and deletions have been reported, mostly in exons 10, 11, 12, 13, 14, 17 and 21. For example, mutation screening in a nevoid basal cell carcinoma patient showed a novel nonsense mutation in PTCH (c.1136 C→G; p.Ser383X).⁶ In an Italian study, 13 novel mutations were reported, including p.T230P, p.F505_L506delinsLR, and many others.⁴ Marsh et al.³ used denaturing high-performance liquid chromatography to screen for PTCH mutations in 28 nevoid basal cell carcinoma cases, and found protein truncations ($n=10$) and missense or insertion-deletion ($n=4$)

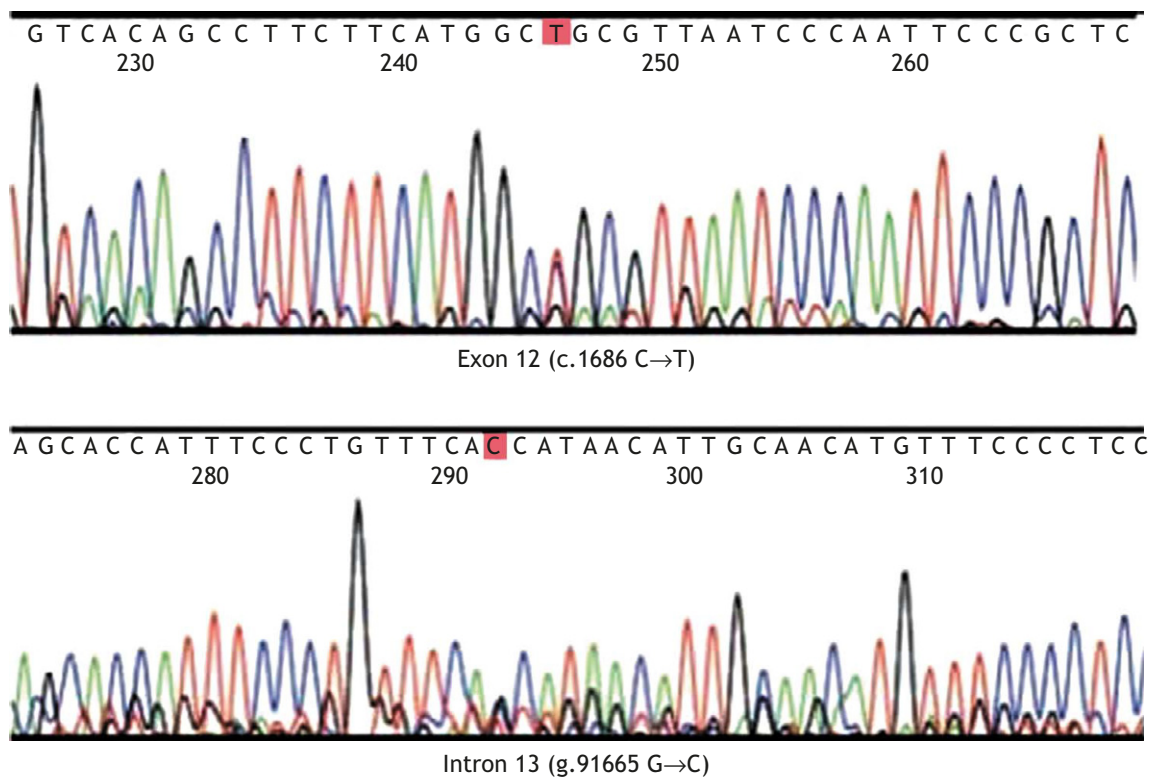


Fig. 9 Genomic DNA obtained from the patient for the PTCH gene sequencing procedure. A transition of C→T was observed in exon 12 (c.1686bp) (in red) and a G→C in intron 13 (g.91665bp) (in red).

mutations in 14 of 28 (50%) cases, while an additional case carried an unclassified variant, c.2777 G→C. Among the mutations, 13 of the variants were novel, and the mutation frequency was similar in inherited and de novo cases. Gu et al.⁷ investigated 10 non-syndrome associated keratocysts and two cases associated with Gorlin syndrome. Four novel and one known PTCH mutations were identified in five individual patients, including two germline mutations (2619 C→A, and 1338_1339insGCG) in two cysts associated with Gorlin syndrome, and three somatic mutations (3124_3129dupGTGTGC, 1361_1364delGTCT, and 3913 G→T) in three non-syndromic cysts. In another study, three Chinese families with sporadic OKCs and nevoid basal cell carcinomas were enrolled, and a mutation analysis was performed by amplifying all exons of the PTCH gene and sequencing the products. The results identified three novel germline mutations in PTCH, including a missense mutation (p.S1089→P) in a sporadic case, a nonsense mutation (p.Q160X) in a syndromic OKC, and a de novo mutation (c.768_777delGACA-AACTTC) in another syndromic OKC.⁸ Besides genetic mutations, many isoforms of PTCH messenger (m)RNA were identified involving exons 1–5, exon 10, and a novel exon 12b.⁹ Since the PTCH product serves as a receptor for SHH, the expressions of PTCH and SHH were detected in 18 sporadic and four

nevoid basal cell carcinoma-associated OKCs, and seven control gingivae by reverse-transcriptase polymerase chain reaction.¹⁰ However, no mutations were identified in the four nevoid basal cell carcinoma-associated OKCs by direct sequencing.¹⁰

A mutation of c.1686bp C→T translating an A562A silent mutation in exon 12 was detected in our case. Exon 12 encodes the transmembrane domain 5 of the PTCH gene and serves as a sterol-sensing domain. However, this mutation was not specific for the development of nevoid basal cell carcinoma. The same mutation was not only reported in nevoid basal cell carcinoma,¹¹ but also in alveolar rhabdomyosarcomas,¹² embryonal rhabdomyosarcomas,¹² medulloblastomas,¹³ basal cell carcinomas from xeroderma pigmentosa,¹⁴ and squamous cell carcinomas.¹⁵

Intronic aberrations of the PTCH gene have previously been reported in many different diseases, including basal cell carcinoma (introns 3, 7 and 19),¹⁶ nevoid basal cell carcinoma (introns 5, 6, 7, 9, 10, 17 and 18),^{11,17–22} multiple self-healing squamous epitheliomas (intron 8),²³ germline DNA of nevoid basal cell carcinoma (intron 9),²⁴ medulloblastomas (introns 5 and 9),^{25,26} Bowen's disease (introns 10 and 15),²⁷ breast carcinomas (intron 10),²⁸ rhabdomyosarcomas (introns 10, 15 and 17),¹² basal cell carcinomas (introns 1, 8, 9, 12, 15 and 19),^{16,29–32} and

medulloblastomas (intron 17).¹³ In our case, a second mutation was found, a G→C at g.91665bp in intron 13, which has not been previously reported. Whether there is any significant functional disturbance due to this intronic mutation remains to be studied.

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